
EDITORIALS

Factors Related to Risk of Penile Cancer: New Evidence From a Study in the Pacific Northwest

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Penile cancer is perhaps the least understood of the anogenital cancers believed to be associated with human papillomavirus (HPV) infection. It is relatively rare in developed countries, with a higher incidence in developing countries such as India, Mexico, and China and among Hindu populations in Bali, where it represents a significant health problem (1). Lack of circumcision at birth and poor genital hygiene have often been posited as playing a role in the etiology of this disease.

In this issue of the Journal, a case-control study (2) implicates several risk factors in patients from western Washington state and parts of western Canada. The observations of Maden et al. (2) provide new evidence to suggest that conditions associated with chronic irritation may play a substantial role in the pathogenesis of penile cancer, and this finding is consistent with our understanding of other forms of anogenital cancer, including anal cancer (3). After adjustment for confounding variables, elevated risk estimates were reported for cigarette smoking, physician-diagnosed genital warts, having 30 or more sexual partners, a rash or tear on the penis, and circumcision at some time other than birth or no circumcision at all (2).

Among uncircumcised men, presence of smegma or difficulty in retracting the foreskin was associated with an elevated risk of penile cancer. For all subjects, history of penile rash showed the strongest association, with a risk estimate of 9.4. The rash may have been the result of irritation or lesion-associated pruritus from the presence of the cancer itself, or it could have represented undiagnosed genital warts or other HPV-associated diseases. It would be of interest to know the temporal relationship between the rash and the diagnosis of the cancer and whether the men who reported a penile rash were those who had evidence of HPV in their tumor tissue.

In the article by Maden et al., elevated risk estimates were reported for current cigarette smoking, with an increase in risk with number of pack-years (2). Smoking has been related to penile cancer in a previous study (4), is a risk factor for anal and cervical cancer (5,6), and has been

reported to be associated with an increased risk for cervical cancer among women whose cervical samples tested positive for HPV type 16 or 18 (6). Both current cigarette smoking and infection with HPV 16 have been shown to have independent detrimental effects on the immune system by diminishing the number of Langerhans' cells in cervical epithelium (7). Reduction in the number of these major antigen-presenting cells, while previously noted in cervical epithelium (7), may also constitute a mechanism that explains the role of smoking in penile cancer.

The 45.5% of the tissues described as carcinoma in situ and the 54.5% described as invasive cancer were combined for analysis in the study by Maden et al. (2). Caution is in order when carcinoma in situ and invasive cancer tissues are combined for analysis, since they may not represent a continuum of the same disease. The natural history of penile carcinoma in situ is not well understood (8) and may represent different diseases with respect to its clinical presentation and likelihood of progressing to invasive cancer (9). Moreover, all carcinoma in situ tissues with bowenoid features were shown to be positive for HPV 16 DNA, whereas those without these features were uniformly negative for HPV 6B, 11, 16, and 18 DNA (10). With a sufficient number of specimens, separate analysis of carcinoma in situ and invasive cancer tissues could yield useful information.

The possible role of HPV in the pathogenesis of penile cancer was proposed after study findings suggested an association between penile cancer and condyloma acuminatum (11). This relationship was corroborated by a case-control study (12) of penile cancer conducted in China, in which physical examination of 71 patients and 71 age-matched control subjects showed that 13 patients versus one control subject had genital warts, with most located at the tumor site. No HPV typing of the lesions was reported. Similarly, Maden et al. (2) reported a strong association between history of genital warts and penile cancer, with a risk estimate of 5.9.

HPV types are often, but not always, associated with distinct clinical and histopathologic entities, such as HPV 16 and 18 with anogenital carcinoma (6,13) and HPV 6 and 11 with genital warts (15). While HPV 16 and 18 may be found in penile warts (14), many anogenital warts contain HPV 6 or 11 (15); the latter are infrequently associated with invasive penile cancer. Therefore, it seems likely that the association between history of genital warts and the development of penile cancer is indirect. For example, HPV 6 and/or 11 that are detected in penile warts may be a marker for higher risk of acquisition of other HPV types specifically associated with cancer. It is interesting that Maden et al. (2) did not find any association between history of genital warts and presence or absence of HPV DNA in the tumor tissue.

The proportion of penile cancer tissues found to be positive for HPV DNA has varied widely in previous studies, with many, but not all, reporting HPV DNA in

*See "Notes" section following "References."

fewer than half of the tissues (10,16-19). Determination of the HPV types found in penile cancer tissue has been facilitated by the advent of techniques that boost the sensitivity of testing (such as polymerase chain reaction) and thus permit the study of formalin-fixed tissues in paraffin sections. Using this technique, Maden et al. detected HPV DNA in 49% of the tumor tissues tested. The HPV types present in the tissues were predominantly HPV 16 (70%), with the remaining HPV types and their prevalences not reported in their article. In other studies (16,17), HPV 18 was found by Southern blot hybridization in 9%-39% of penile cancers in Brazil (16,17), and in one study, no HPV 16 was found in the lesions (17). HPV 54 and HPV 55 also have been described in penile cancers (20). Comparisons among these studies are difficult because they used diverse populations and different laboratory methods.

Similar to cervical cancer, penile cancer may have more than one pathogenic pathway. HPV DNA-positive cervical cancers have been shown to occur in younger women, whereas HPV-negative cervical cancers typically occur in older women (19). Tumors in older women have been associated with mutations that may inactivate the p53 gene (21), which is similar to the effect of binding of p53 by the HPV E6 oncoprotein (22). In the study by Maden et al., it would be of interest to know whether there were age differences among the men whose specimens were HPV positive or negative and whether the negative tumors were associated with mutations in tumor suppressor genes, such as p53.

Because of its association with a sexually transmitted agent, penile cancer has public health implications that extend beyond the affected individuals. Geographical correlations between penile and cervical cancers have been reported in diverse populations (23,24). Associations also have been reported for occurrence of these cancers between husbands and wives (25-27). A high prevalence of HPV-associated penile intraepithelial neoplasia has been found in sexual partners of women with cervical intraepithelial neoplasia (28). It would be relevant to study cervical material from wives of men with penile cancer at the time of diagnosis to screen for HPV by type and for pathologic changes.

The results of the study by Maden et al. (2) support public health interventions that could diminish the incidence of penile cancer. Vigilant efforts to discourage smoking should be maintained as a general public health measure that also could have a modest effect on the risk of penile cancer. The results obtained by Maden et al. corroborate previous work that demonstrated an association between lack of neonatal circumcision and the development of penile cancer. However, the new study reported circumcision at birth in 20% of the men with penile cancer. The recommendation of circumcision for medical indications remains somewhat controversial, and as with all medical procedures, the risks and benefits must be weighed.

The available evidence suggests that penile cancer, similar to other anogenital cancers (3,5-7,13), is the final result of a chronic process that includes several distinct factors. To better understand the pathogenesis of this disease, the

interplay between HPV, chronic irritation, circumcision, smoking, and genetic factors must be considered in future studies. The study by Maden et al. (2) provides another meaningful step in this direction.

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Second Cancer After Hodgkin's Disease—The Price of Success?

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The treatment of Hodgkin's disease is one of the triumphs of modern cancer therapy. Forty years ago, the average patient had a life expectancy of less than 3 years. Today, approximately three out of every four patients are curable (1). This dramatic change in survival was made possible by the development of supervoltage x-ray therapy machines in the 1950s and 1960s and the subsequent introduction of combination chemotherapy. As a result of this phenomenal success, the long-term complications of treatment have assumed clinical importance. They include cardiopulmonary disease, sterility, thyroid dysfunction, altered immunity, and second cancer (2).

By far the most serious consequence of curative therapies for Hodgkin's lymphoma is the heightened risk of developing a new cancer. Twenty years ago, secondary cancer was first recognized as a life-threatening effect of treatment (3). Excess acute leukemia was observed early and was generally ascribed to chemotherapy. Non-Hodgkin's lymphoma was then reported to occur with increased frequency, probably as a result of disease-related or treatment-induced immunosuppression (4). As patients survived for longer periods, solid tumors, thought to be radiation related, surpassed the hematologic malignancies in absolute terms as the major hazard of successful treatment. About one of every six patients with Hodgkin's disease is likely to develop a second cancer within 15 years of treatment (5,6).

In this issue of the *Journal*, Hancock and colleagues (7) present convincing evidence that breast cancer is a serious complication of aggressive therapy for Hodgkin's disease. Among 885 women treated between 1961 and 1990 at Stanford University Medical Center, 25 patients developed breast cancer, whereas only about six cancers would have been expected on the basis of general population rates. All

25 patients had received radiotherapy that resulted in substantial exposure of breast tissue to radiation.

Overall, a threefold risk of breast cancer was apparent 5-9 years after treatment, increasing to more than 10-fold among 20-year survivors. There was a striking change in risk according to age at treatment, with no excess risk observed among the 300 women who were older than 30 years when they received irradiation. Otherwise, absolute risks were similar by age at exposure—three to four extra breast cancers per 1000 women per year.

Women treated under age 20, whose follow-up periods included ages with normally low breast cancer risk, were at much higher relative risk (RR) than women who were treated in their twenties. Radiation risk coefficients were calculated on the basis of the mantle dose, 40-47 Gy, which probably overestimates the actual dose to breast tissue. Nonetheless, the computed RR at 1 Gy (1.2-1.9) is similar to that observed in other studies of women exposed to ionizing radiation (8). In the study by Hancock et al. (7), there was a suggestion that chemotherapy with alkylating agents may have enhanced the breast cancer risk due to radiotherapy during the first 15 years after treatment. Death attributable to breast cancer was also significantly increased.

Radiotherapy was first used to treat Hodgkin's disease in 1902 (9), but it was the pioneering studies at Stanford University Medical Center that formed the basis for prevailing views about the curability of this disease (10). The present study from Stanford (7) carefully evaluates late complications of treatment and reinforces current understanding of radiation-induced breast cancer. Other than radiation dose, age at exposure is seen as the most important determinant of risk, with risk decreasing as age at exposure increases. Once the minimum 5-year latent period for radiation-induced solid tumors is passed, risk increases, perhaps to very high levels. The study by Hancock and associates (7) is the first to quantify the carcinogenic potential of very high radiation doses (>10 Gy) and raises the possibility that chemotherapy may have contributed to the high breast cancer risk. The value of careful surveillance was apparent in that more than half of the breast cancers were unknown to the patients and were detected during routine follow-up examinations.

Of special clinical interest is the finding that risk increased dramatically over time. For patients with more than 15 years of follow-up, the RR of breast cancer was

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